Atty. Docket No. BRI010 P300

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Art Unit	:	1612
Examiner	:	Barbara P. Badio
Applicant	:	Verlan H. VanRheenen
Appln. No.	:	10/815,351
Filed	:	April 1, 2004
Confirmation No.	:	8270
For	:	CRYSTALLINE 19-NORSTEROIDS

TRANSMITTAL OF APPEAL BRIEF
(PATENT APPLICATION - 37 CFR §41.37)

1. Transmitted herewith is the APPEAL BRIEF in this application, with respect to the Notice of Appeal filed on November 14, 2008.

2. **STATUS OF APPLICANTS**

This application is on behalf of:

___ other than a small entity.

_X_ a small entity.

3. **FEE FOR FILING APPEAL BRIEF**

Pursuant to 35 USC §41(a)(6), the fee for filing the Appeal Brief is:

___ small entity	$270.00
___ other than a small entity	$540.00
Appeal Brief fee due:	$270.00

4. **EXTENSION OF TERM**

The proceedings herein are for a patent application and the provisions of 35 USC §41(a)(8) apply.

(b) _X_ Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition and fee for extension of time.

5. TOTAL FEE DUE

The total fee due is:

Appeal Brief fee:	$270.00
Extension fee (if any)	$ 0.00
TOTAL FEE DUE:	$270.00

6. FEE PAYMENT

___ Attached is a check in the sum of $_____.

X Charge fee to Credit card the sum of $270.00.

7. FEE DEFICIENCY

X If any additional extension and/or fee is required, this is a request therefor and to charge Account No. 16 2463.

and/or

X If any additional fee for claims is required, charge Account No. 16 2463.

Respectfully submitted,

January 14, 2009
Date

/Gunther J. Evanina/
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
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Dear Sir:

APPEAL BRIEF (37 CFR §41.37)

This brief is in furtherance of the Notice of Appeal, filed in this case on November 14, 2008.

The fees required under 35 USC 41(a)(6), and any required petition for extension of time for filing this brief and fees therefor, are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This brief contains these items under the following headings, and in the order set forth below (37 CFR §41.37(c)):

I. Real Party in Interest

II. Related Appeals and Interferences

III. Status of Claims

IV. Status of Amendments

V. Summary of Claimed Subject Matter

VI. Ground of Rejection to Be Reviewed on Appeal

VII. Arguments

VIII. Conclusion

Appendix of Claims Involved in the Appeal

Evidence Appendix

Related Proceedings Appendix

The final page of this brief bears the attorney's signature.

I. Real Party In Interest

The real party in interest in this application is Bridge Organics Co., a corporation of the state of Michigan having a place of business at 311 W. Washington St., Kalamazoo, Michigan 49097. An assignment of the application to the real party in interest (Bridge Organics Co.) was recorded at Reel 015180, Frame 0400.

II. Related Appeals And Interferences

There are not any related appeals or interferences which will directly affect, or be directly affected by, or have a bearing on, the Board's Decision in this Appeal.

III. Status Of Claims

This is an Appeal from the rejection of claims 1-4. Claims 1-4 are pending and under consideration in the application. There are not any claims that have been canceled or withdrawn from consideration.

IV. Status Of Amendments

There have not been any amendments filed after the Final Rejection of claims 1-4 in an Office Action having a mailing date of August 18, 2008. The appending claims are believed to be an accurate listing of the claims under appeal.

V. Summary Of Claimed Subject Matter

Independent claims 1 and 3 are under appeal.

Independent claim 1 is directed to 17α-Acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione hydrochloride. The name of the compound set forth in claim 1 is itself a complete description of the chemical structure of the compound. The pharmaceutical utility of the claimed compound as an antiprogestational agent is set forth at page 2, lines 23-24 (paragraph 0009) of the specification. A detailed description of a technique for making the claimed compound is provided at page 3, line 22 through page 4, line 2 (Example I, paragraph 0021).

Independent claim 3 is directed to 17α-Acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione hydrobromide. The name of the compound set forth in claim 3 is itself a complete description of the chemical structure of the compound. The pharmaceutical utility of the claimed compound as an antiprogestational agent is set forth at page 2, lines 23-24 (paragraph 0009) of the specification. A detailed description of a technique for making the claimed compound is provided at page 4, lines 3-12 (Example II, paragraph 0022).

VI. Ground Of Rejection To Be Reviewed on Appeal

Claims 1-4 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Kim et al. (United States Patent Application Publication No. 2002/0025951 or a corresponding application filed pursuant to the Patent Cooperation Treaty and published as WO 01/47945) in view of Berge et al. ("Pharmaceutical Salts," Journal of Pharmaceutical Sciences, Vol. 66(1), pages 1-19, 1977).

VII. Arguments

The Final Rejection states that "[b]ecause hydrochloride and hydrobromide salts are well known salts in the pharmaceutical art and said salts of steroids are well known (see for example, US 4,451,405, Examples 6-10; US 3,723,523, Example L), the hydrochloride and hydrobromide salts of 17α-Acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione as taught by Kim would have been obvious to the skilled artisan in the art."

There is not a shred of evidence in the record to support the rejection. Appellant admits that the prior art when taken as a whole leads the person of ordinary skill in the art to expect that salts forms, and particularly crystalline salt forms, of pharmaceutically active compounds, including steroids, may have desirable properties. In fact, in many cases, as is the case with the claimed compounds, the difference between the base compound and a salt form can be critical to providing benefit of the therapeutic efficacy of the compound to the public. For example, as is the case with the claimed compounds, developing sufficiently economical techniques of

adequately purifying the compounds for regulatory approval and commercial use can be elusive and prevent commercialization of the product.

Appellant admits that the desirability of salts forms of the 19-norsteroid compounds disclosed by Kim et al. would have been immediately recognized by those having ordinary skill in the art. However, the obvious desirability of developing a salt form of the 19-norsteroid compounds of Kim et al. is itself evidence of non-obviousness. Kim et al. undoubtably attempted to make such compounds prior to the filing of their application, but apparently were not able to do so.

The science fiction literature is replete with visions of highly desirable technologies. However, the desire for a thing does not necessarily make it obvious. It is not enough that the prior art leads the person of ordinary skill in the art to expect that an envisioned compound could, if it can be brought into existence, provide some potential benefit. An invention is not obvious unless it is obvious how the invention can be made. Discovering how to make a desired compound that did not previously exist can form the basis for patentable inventions, including both the process and the compound itself.

In the case of the claimed invention, patent protection for the process disclosed in the specification would be essentially meaningless. Once the previously unacquirable compound is acquired, such as by purchasing materials made by Appellant, it can be used as a seed material for easily crystallizing more of the compound, as is well known in the art.

Beckman Instruments, Inc. v. LKB Produkter AB, 892 F.2d 1547, 1551 (Fed. Cir. 1989), citing *In re Payne*, 606 F.2d 303, 314 (C.C.P.A. 1979), states that "[i]n order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method." The reference to "apparatus or method" was made merely because the patent at issue concerned methods and apparatus. There is not any reason to restrict this principle to apparatus and methods. To the contrary, the patent laws apply uniform standards of patentability to all categories of statutorily authorized inventions. Accordingly, Appellant's claimed compounds would not have been obvious unless the prior art enables one of ordinary skill in the art to make the claimed compounds. Thus, the law mandates issuance of a patent for the claimed invention unless the prior art teaches or makes it obvious how to produce the claimed compounds.

Kim et al. teach nothing about Appellant's claimed salt forms of 19-norsteroid compounds or how such compounds might be made. The Examiner has never made the slightest suggestion to the contrary. Berge et al. disclose that various salt forms may have advantages relating to such things as lower cost, purification and processing, but do not provide any teaching concerning preparation of pharmaceutically active salts. The Examiner has never made the slightest suggestion to the contrary.

Rather than explaining how the prior art enables the person of ordinary skill in the art to make the claimed compounds, the Examiner has argued that "[t]he issue is not the method of making the claimed salts but whether said salts would have been obvious to the skilled artisan in the art at the time of the present invention." There is not any evidence on the record that the claimed invention is enabled by the prior art. Instead, it is the Examiner's position that the failure of the prior art to enable Appellant's claimed invention is simply irrelevant.

Thus, it is submitted that this appeal must be resolved based on a determination of two questions: (1) does the law require that the prior art underlying an obviousness rejection enable the person of ordinary skill in the art to make the claimed compounds; and (2) does the weight of evidence support a finding that the prior art does not enable the claimed invention. It is further submitted that each of these questions must be answered in the affirmative.

Unquestionably, Beckman makes it clear that an obviousness rejection cannot be sustained if the prior art upon which the rejection is based does not enable the person of ordinary skill in the art to make the claimed invention. The Examiner has not cited any authority to the contrary. As stated in the case of *In re Payne*, the "[r]eferences relied upon to support a rejection under 35 U.S.C. §103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public." An invention cannot be possessed absent some known or obvious way to make it. *In re Hoeksema*, 399 F.2d 269, 274 (C.C.P.A. 1968). A different law, as proposed by the Examiner, would be unjust to both inventors and society, as it would divert efforts away from discovering how to make compounds that could benefit society whenever a proposed compound is published, irrespective of whether it is known or obvious how to make such compounds. Such law would be clearly contrary to the commerce clause of the United States Constitution, which authorizes Congress to establish a patent system to promote, not impede, the useful arts.

It is submitted that the laws unquestionably require an obviousness rejection be supported by prior art that enables the person of ordinary skill in the art to make the invention defined by the rejected claims. The only remaining question is whether the evidence of record is sufficient to support a conclusion that the prior art does not teach or make it obvious how to prepare Appellant's claimed compounds.

Appellant has provided substantial evidence of non-obviousness in the attached Declaration of Verlan H. Van Rheenen (Exhibit 1). This declaration shows that it was not known, nor obvious, how to make the claimed salts, and that only after numerous failures and considerable trial and error did Appellant discover an unorthodox approach for making the clamed salts. This evidence shows that the combined teachings of the applied prior art references (Kim et al. in view of Berge et al.) did not make any method of preparing the claimed salt obvious. There is not any evidence supporting a finding that the prior art teaches how to make the claimed compounds or that the person of ordinary skill in the art would have found such method obvious. The Examiner has not even alleged that there is any such evidence. Rather, the Examiner has taken the position that the law does not require consideration of Appellant's evidence of non-obviousness because it is not relevant to patentability whether the applied prior art teaches how to make the claimed invention.

Thus, the evidence overwhelmingly demonstrates that the prior art does not enable the person of ordinary skill in the art to make the claimed compounds, and as such does not place the claimed invention in the possession of the public, and therefore does not make the claimed invention obvious under 35 U.S.C. §103.

Therefore, the rejection is based on an error or law, namely that the prior art need not enable a claimed invention and place the invention in the possession of the public in order to render the claimed invention unpatentable, and a failure to properly consider Appellant's evidence demonstrating that the invention is not obvious. Contrary to the Examiner's preference, such evidence cannot properly be ignored. Rather, MPEP §2141(V) correctly advises that "Office personnel should consider all rebuttal evidence that is timely presented by the Applicants when reevaluating any obviousness determination." Indeed, it is always error to exclude evidence of secondary indications of non-obviousness from consideration. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530 (Fed. Cir. 1983).

It is respectfully submitted that the Board of Patent Appeals and Interferences should reverse the rejection of claims 1-4 because the record includes an abundance of evidence which establishes that the prior art of record (which teaches nothing about making Appellant's claimed compound) does not place the claimed compounds in the possession of the public, and does not make the claimed salts obvious under 35 USC §103.

VIII. Conclusion

Upon thorough consideration of the evidence and relevant laws, it is believed that the Board of Patent Appeals and Interferences will find that the claims under appeal are patentable over the teachings of Kim et al. in view of Berge et al. Accordingly, a reversal of the rejection is requested.

Respectfully submitted,

January 14, 2009
Date

/Gunther J. Evanina/

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Appendix of Claims (37 CFR §41.37(c))

1. 17α-Acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione hydrochloride.

2. A compound according to claim 1 which is 17α-Acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione hydrochloride in crystalline form.

3. 17α-Acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione hydrobromide.

4. A compound according to claim 3 which is 17α-Acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione hydrobromide in crystalline form.

Evidence Appendix (37 CFR §41.37(c))

Exhibit 1 is the Declaration of Verlan H. Van Rheenen, entered into the record with the Request For Continued Examination (RCE) and Amendment having a mail room date of June 2, 2008.

EXHIBIT 1

Atty. Docket No. BRI10 P-300

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Examiner	:	Barbara P. Badio
Applicant	:	Verlan H. VanRheenen
Appln. No.	:	10/815,351
Filing Date	:	April 1, 2004
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For	:	CRYSTALLINE 19-NORSTEROIDS

Dear Sir:

DECLARATION OF VERLAN H. VAN RHEENEN

I, Verlan H. Van Rheenen, hereby declare the following:

1. I am the inventor of the above-identified U.S. Patent Application No. 10/815,351, filed April 1, 2004, entitled "CRYSTALLINE 19-NORSTEROIDS."

2. I am currently the Vice President of Research and Development of Bridge Organics Company, the assignee of the above-identified U.S. Patent Application No. 10/815,351.

3. Bridge Organics Company is a research company engaged in the preparation of complex organic compounds and in the development of chemical processes for scale up. (Attached Exhibit A is a brochure describing Bridge Organics Co. and its services).

4. Prior to working for Bridge Organics Company, I was employed at Pharmacia & Upjohn, Kalamazoo, Michigan from 1966 to 1997. During my employment at Pharmacia & Upjohn, I was primarily engaged in research and development relating to steroid production, including synthesis and purification.

5. I earned by Doctor of Philosophy in organic chemistry from the University of Wisconsin, Madison, in 1966.

6. A copy of my circular vitae is attached hereto as Exhibit B.

7. I have read the Office Action dated August 3, 2007, in which all of the pending claims (1-4) of U.S. Application No. 10/815,351 were rejected under 35 U.S.C. §103(a) over Kim et al. (U.S. Patent Publication No. 2002/0025951 or WO 01/47945) in view of Berge et al. ("Pharmaceutical Salts," *Journal of Pharmaceutical Sciences*, January 1997, Vol. 66, No. 1).

8. I have read and understand the teachings of the applied Kim et al. and Berge et al. references.

9. The Office Action correctly states that the Kim et al. reference discloses the free base of the claimed hydrochloride and hydrobromide salts, and that the Berge et al. reference discloses that the characteristics of medicinal agents can be manipulated and optimized by converting a pharmaceutically active free base compound to a salt form.

10. It is my opinion that these disclosures would not have made the claimed compounds obvious to a person of ordinary skill in the art at the time the invention was made.

11. During my experiences as a scientist and researcher in the pharmaceutical arts, I have on occasion unsuccessfully attempted to convert a free base to a salt form. Based on these experiences, it is my opinion that it is not always obvious that any particular organic compound having pharmacological activity in its free base form can be converted into a salt form or into any particular salt form. Based on these experiences, I can further state that it is my opinion that the applied prior art references do not teach how to make the claimed salts, nor do they provide any expectation that the claimed salts can be made.

12. Based on my experience and education, it is my opinion that when a person of ordinary skill in the art desires to convert a base compound exhibiting a pharmaceutical activity into a salt form, the person of ordinary skill in the art will attempt to dissolve the free base in a solvent, add an acid compound, and employ some combination of cooling, stirring, seeding, or addition of an anti-solvent to induce precipitation of a salt. However, the outcome is not predictable, and success, if it is even possible, may depend on the solvent or solvents employed, the reagent selected to form the salt, the purity of staring material, and various other parameters, such as temperature and the degree of agitation.

13. I have unsuccessfully attempted to prepare the citrate, methane sulfonic acid, tartrate, and sulfate salts of 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione. I am also personally aware of the numerous unsuccessful attempts of a former employee at Bridge Organics Company, Chiu Hong Lin, to make various other salts of 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione. I have also had several unsuccessful attempts at preparing the claimed hydrochloride and hydrobromide salts.

14. My discovery of the claimed hydrochloride salt was not straight forward, and involved an unusual, and non-obvious combination of parameters. In particular, I discovered that when anhydrous hydrogen chloride in ether was added to the free base dissolved in ethyl acetate an oil deposit was formed. I further discovered that the oil deposit could be solubilized with acetone and re-formed as an oil by adding ether. I further discovered that the oil deposit could be redissolved in acetone, and that upon addition of ethyl acetate and ether, precipitation of

an amorphous solid occurred. Upon stirring at 40°C, the amorphous solid was slowly converted into a white, crystalline solid which was filtered and washed with ethyl acetate. Analysis showed that this crystalline solid was distinct from the starting free base material.

15. It is my opinion that the combination of steps, solvents, and parameters needed to made 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione hydrochloride is not obvious, and that the person of ordinary skill in the art would likely have become discouraged. In particular, it is my opinion that the person of ordinary skill in the art would have likely thought that the experiment was a failure upon formation of an oil deposit and would not have found it obvious to redissolve the oil deposit in acetone, add ethyl acetate, and add ether to cause precipitation of an amorphous material. Further, it is my opinion that the person of ordinary skill in the art would likely have regarded the precipitation of an amorphous material a failure and abandoned the experiment. Further, it is my opinion that the person of ordinary skill in the art would not have found it obvious to continue stirring the amorphous material in the combination of solvents at 40° to slowly convert the amorphous material to the claimed crystalline salt.

16. In the case of the hydrobromide salt, after various attempts resulted in the formation of an oil phase, crystals were finally obtained by dissolving the oil in acetone, adding ethyl acetate to the turbidity point, and then seeding with a trace of the previously isolated hydrochloride salt. This resulted in crystallization of the hydrobromide salt. Accordingly, I did not obtain the hydrobromide salt without first obtaining the hydrochloride salt by an unusual process that would not, in my opinion, have been obvious to a person of ordinary skill in the art.

17. From my experience, it is generally desirable to provide pharmaceutically active compounds in a crystalline form in order to facilitate economical purification, to establish quality criteria, and to achieve regulatory approval (i.e., FDA approval) of a commercially viable product.

18. In my experience, the ability to make a pharmaceutical product available to the benefit of the public often hinges on the discovery of a suitable crystalline salt form of the active ingredient. This, in my opinion, is the case with 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione which, in its free base form, is not crystalline. Clinical trials on human subjects strongly suggest that this compound is useful and highly beneficial when administered for the treatment of endometriosis, dysmenorrhea, endocrine hormone-dependent tumors, uterine fibroids, and endometrial proliferation.

19. However, it is my understanding that 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione cannot be exploited unless it can be made available in an economically purifiable form. Unless a pharmaceutical product can be made in an approved form at a reasonable price, it cannot be brought to market and it cannot be made available to the benefit of the public.

20. Hyun Kim et al. filed their first patent application disclosing 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione on May 1996. The antiprogestational activity of the compound and a method of making the compound were published in WO 97/41145 on November 6, 1997. Thus, those of ordinary skill in the art would have been aware of the compound and its purported utility in 1997.

21. It is also my opinion that those of ordinary skill in the art would have been aware of the desirability and need for providing 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione in a crystalline salt form. This is demonstrated by the Berge et al. reference, which describes advantages for providing a compound in a crystalline salt form.

22. It is also my opinion that a person of ordinary skill in the art would have understood that the discovery of a suitable crystalline salt form of 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione would likely be critical in bringing a product to market that could benefit the public. In other words, it is my opinion that Kim et al. and those of ordinary skill in the art would have been aware of the urgent need to discover a suitable crystalline salt form of the compound, at least as early as about 1997.

23. It is my opinion that the very fact that the Kim et al. publication does not disclose a crystalline form of the compound suggests that Kim et al. were unable to discover a method of forming a crystalline form of the compound, since such crystalline form would have been advantageous for purification and testing purposes within the scope of their disclosure.

24. The recognized importance of 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione is demonstrated by the subsequent efforts of Kim et al. to develop improved methods of making this specific compound, as indicated in WO 01/47945. This document is focused on achieving improved yield for the compound.

25. Since filing their first application in 1996, Kim et al. have filed five related applications in the United States alone. Despite a long recognized need for a suitable crystalline salt of 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione, none have been disclosed in the literature until Applicant's discovery of the hydrochloride and hydrobromide salts of this compound were disclosed on October 6, 2005 in U.S. Patent Application Publication No. 2005/0222109.

26. The Berge et al. reference only discloses the desirability of making crystalline salt forms of pharmaceutically active compounds, and does not enable those of ordinary skill in the art to make the salt forms. The Berge et al. reference merely discloses the 53 anions that had been employed in FDA approved commercially marketed salts as of January 1977. While the Berge et al. reference indicates that hydrochloride salts forms are the most utilized form, it does not disclose how to make the hydrochloride form of 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione or any other active agent.

27. In my opinion, the person of ordinary skill in the art would not have known from the Kim et al. and Berge et al. references how to make the claimed hydrochloride or hydrobromide forms of the 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione compound disclosed by Kim et al.

28. It is my opinion that the approximately seven year period between the disclosure of 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione by Kim et al. in 1997 and my discovery of the hydrochloride and hydrobromide forms of this compound in 2004 is evidence of a long-felt, but unfulfilled need for the claimed salts.

29. Further, it is my opinion that it can be reasonably inferred that Kim et al. and likely others, attempted, but failed to make the claimed crystalline salts or any other salt forms of 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione. We (myself and others at Bridge Organics Co.) have also failed on many occasions over a period of years to successfully prepare a crystalline form of the free base.

30. The Berger et al. reference is concerned primarily with developing techniques for selecting the most appropriate salt form of a pharmacologically active compound when two or more forms of the compound of interest have already been discovered. It does not provide any teaching relevant to how such discovery of salt forms can be made.

31. Based on the teachings of Kim et al. in view of Berge et al., the person of ordinary skill in the art would not know whether 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione can be converted into a salt form, and if so which particular salt form(s), or how such salt form(s) might be made.

32. The combination of Kim et al. in view of Berge et al. establish an urgent need for a salt form of 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione, but do not provide any guidance toward how such salts may be prepared.

33. The combination of Kim et al. in view of Berge et al. establish the desirability of converting the 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione compound to a salt form. It is my opinion that the failure of Kim et al. to disclose a crystalline form of the compound is evidence that they were unable to make a crystalline form of the compound. These failures coupled with my own failures and that of my

colleague, Chiu Hong Lin, are evidence that the claimed salts would not have been obvious to a person of ordinary skill in the art.

The undersigned hereby declare that all statements made herein of their own knowledge are true and that all statements made on information and belief are believed to be true; and further, these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

By: Verlan H. VanRheenen
Verlan H. Van Rheenen

May 30, 2008
Dated

EXHIBIT A

KEY PERSONNEL BIOGRAPHIES

Edward J. Hessler, Ph.D.
President
Specialist in peptide, steroid and heterocyclic research.

Harold A. Karnes, Ph.D.
Vice President, Sales
Specialist in prostaglandins and heterocyclic research.

Verlan Van Rheenan, Ph.D.
Vice President, R & D
Specialist in steroid and prostaglandin research.

Max E. Breuer, Ph.D.
Vice President, Engineering
Specialist in separation processes and process development.

David R. Buss, Ph.D.
Vice President, Finance
Specialist in scaleup of complex reactions and fermentation isolations

Bridge Organics Co

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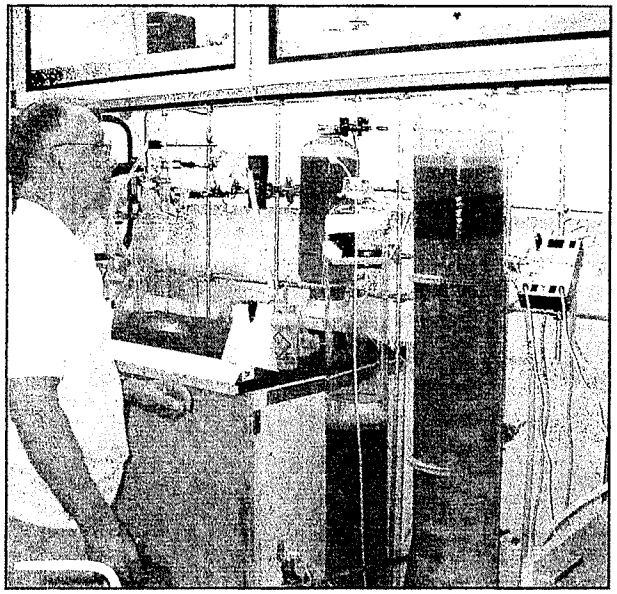
BRIDGE ORGANICS COMPANY

Bridge Organics is a research company engaged in preparation of complex organic compounds and in developing chemical processes for scaleup.

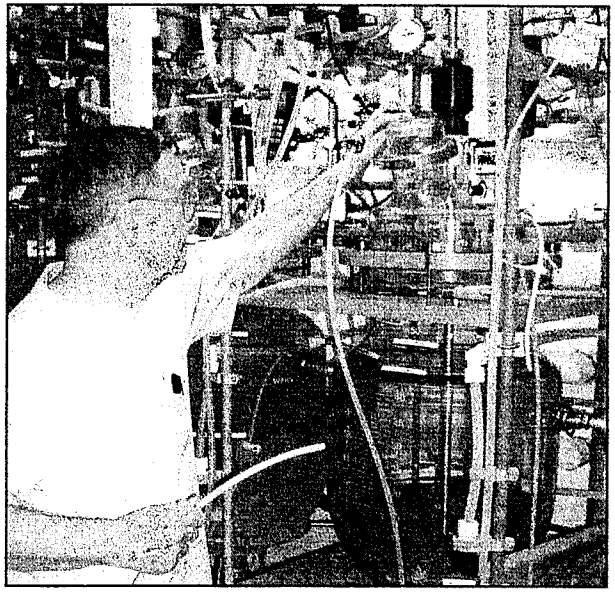


The company, which began operations in November 1997, was founded by retired scientists managers from Pharmacia & Upjohn. The founders had over 140 combined years of experience in chemical operations, first as scientists in process R&D and preparation laboratories, then as managers in chemical operations, including preparations, R&D, purchasing, chemical marketing, chemical production, and materials planning.

Bridge Organics is located in a 9,400 square foot R&D facility which is superbly suited for organic chemical and engineering research. Our equipment includes an HPLC, a 250 Mhz NMR spectrometer, a polarimeter, a GC, an ozone generator, and many low-temperature circulating coolers.

PREPARATION SERVICES

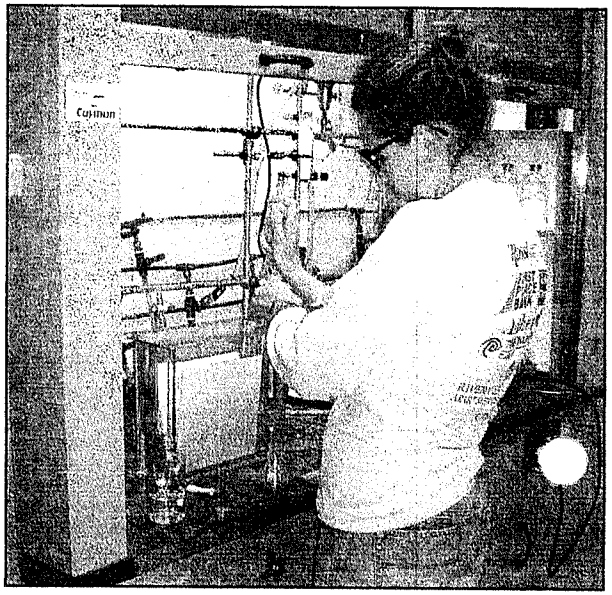
The company's preparation service provides laboratory-scale chemicals of interest to pharmaceutical and biotechnology companies. We can provide batches up to 10 kg or more, with typical purities of 98%. These products, made through complex multi-step laboratory processes, include metabolites, analytical impurities, research materials, stable isotope-labeled chemicals, and chemical library replacements or additions. We have 2 x 50 Liter workcenters, and 1 x 25 Liter workcenter.



Normally, a customer provides an approximate procedure for the reaction sequence, with or without a secrecy agreement (as preferred by the customer).

PROCESS R&D SERVICES

Our scientist are specialists in the design, development and engineering of chemical processes for scaleup purposes. We offer this service to those companies who would like to develop a new process or would like to improve their particular process for manufacturing a chemical (primarily to increase capacity or reduce costs), but who do not have R&D personnel available for such a task. For R&D services, a customer typically provides available process information through a secrecy agreement.



311 W. Washington Street
Vicksburg, Michigan 49097-1200
(269) 649-4200 • Fax (269) 649-0611
www.bridgeorganics.com
bridgeorganics@sbcglobal.net

EXHIBIT B

VERLAN VAN RHEENEN, PH.D.

2117 SHEFFIELD

KALAMAZOO, MI 49001

269-226-9660

BRIDGE ORGANICS CO.

Vice President of Research and Development 1998-current

Experience in many areas of organic synthesis.

UPJOHN CAREER SUMMARY

Extensive experience in primary (API) manufacturing: first as a scientist, designing and developing novel practical processes for Production at Pharmacia & Upjohn, and more recentlyn R&D management, concentrating on resource allocation, project management, regulatory compliance, and validation.

Experience and Accomplishments

Pharmacia & Upjohn, Kalamazoo, Michigan 1966-1997

Director, Chemical Process R&D (1984-1997)

- Directed a group of 70-75(~24 Ph.D. scientist-led groups) responsible for design, development, engineering and piloting chemical processes, and installation and maintenance of these processes in a Production Plant.
- Introduced new manufacturing process for many steroid products, both old and new, that transformed P&U steroid technology to one based on sitosterol as raw material.
- Designed and introduced the first manufacturing process for a cephalosporin at Upjohn.
- Actively involved in the design and the construction of a state-of-the-art building for CPR&D. This $20MM project was concluded under budget.
- Devised a Validation Plan for completing Process Qualification (PQ) for over 100 API's being manufactured at P&U.
- Set up an R&D-based Validation Team who devised the work processes and documentation required to satisfy the regulation for PQ and then did the document

preparation and coordination of the Validation Exercise to accomplish the Validation Plan.

- Set up a Process Safety Management system and team to provide the documentation (Process Safety Information Report) to satisfy the OSHA directive and assist in HAZOP analysis for Operational Qualification (OQ).
- Set up a team-based Project Management system for coordination of the many regulatory and logistical issues surrounding a successful API development and manufacturing startup, promoting interaction with other Project Management areas and clear delineation of the responsibilities with line management.
- Introduced Customer Service as a potent marketing tool for the Pharmaceutical Chemical Business

Director, chemical preparations (1992-1993)

Responsible for a group of 34 (~20 scientists) and the Pilot Plant who supplied all APIs needed for preclinical and clinical testing of human and animal hearth products.

Distinguished Scientist V (1977-1984)

* Appointed to the first group of scientists to attain this rank. Remained on the Scientist V committee by appointment throughout my managerial career.
* Developed numerous processes to transform P&U's steroid processing to the sitosterol raw material base.
* Served twice as Interim Associate Director-Chemical Process R&D (1974-1975 and 1983-1984), taking responsibility for a Chemical Section (7-8 Ph.D.-led groups) concurrently with maintaining my chemical laboratory.

Scientist I through Scientist IV (1966-1977)

* Developed novel and economically superior chemical processes for existing products including medroxy progesterone-Provera ®, methyl prodnisolone-Medrol ®, progesterone, prednisolone-Deltasone ®.
* Developed processes for new proprietary products including prostaglandin total synthesis for PGF2a (Prostin F2a®) , PGE2 (Prostin E2® , Dinoprostone®), PGE1 (Prostin VR®, Caverject®), 15a-methyl PGF2a (Methaprost®), and Ibuprofen (Motrin ®).
* Continued involvement through engineering, piloting, plant introduction, and maintenance and improvement of the plant process for the life of the product. See the Publication section for a scientific account of these projects.

Publications

Verlan H. Van Rheenen, "Approaches to a Synthesis of Miroestrol," Ph.D. Thesis, University of Wisconsin , 1966.

Hans Muxfeldt, Manfred Weigele, and Verlan Van Rheenen, "Magnesium Methoxide Cyclization of Biacetyl Derivatives," *J. Org. Chem.* **30** , 3573 (1965).

Verlan Van Rheenen, "Copper Catalyzed Oxygenation of Branched Aldehydes--An Efficient Ketone Synthesis," *Tetrahedron Letters* , 985 (1969).

V. Van Rheenen, "Copper-catalyzed Oxygenation of Enamines, " *Chem. Comm.,* 314 (1969).

Robert C. Kelly, Verlan Van Rheenen, I. Schletter, M.D. Pillai, "Prostaglandin Synthesis. I. An Improved Synthesis Through Bicyclo[3.1.0]hexane Intermediates," *J. Amer. Chem. Soc.,* **95**, 2746 (1973).

R. Kelly and V. Van Rheenen, "Prostaglandin Synthesis. II. A Novel Resolution of Aldehyde and Ketone Intermediates," *Tetrahedron Lett.,* 1709 (1973).

R. Kelly and V. Van Rheenen, "Prostaglandin Synthesis III. An Improved Opening Of Bicyclo[3.1.0]hexane Intermediates." *Tetrahedron Lett., 1067 (1976).*

V. Van Rheenen, R.C. Kelly and D.Y. Cha, "An Improved Catalytic OsO4 Oxidation of Olefins to cis-1,2-Glycols Using Tertiary Amine Oxides as the Oxidant," *Tetrahedron Lett.* 1973 (1976).

V. Van Rheenen, D.Y. Cha, and W.M. Hartley, "Catalytic Osmium Tetroxide Oxidation of Olefins: Preparation of cis-1,2-cyclohaxanediol," *Organic Synthesis,* **58**, 43 (1978).

Verlan Van Rheenen, K. Paul Shephard, "New Synthesis of Cortico Steroids from 17-Keto Steroids: Application and Stereochemical Study of the Unsaturated Sulfoxide-Sulfenate Rearrangement" *J. Org. Chem.*, **44**, 1582 (1979).

US Patents

Joel E. Huber, Verlan H. Van Rheenen, "16α-Methylation of Corticoids" *USP 4990612* (1991)

Joel E. Huber, Verlan H. Van Rheenen, "16α-Methylation Process--Copper Catalysis, Silation" *USP 4929395* (1990).

Joel E Huber, Verlan H. Van Rheenen, "16 α- Methyl-17α- 20-Epoxysteroid and Process" *USP 4891426* (1990).

Verlan H. Van Rheenen, "11β,17α-Dihydroxy-17β-Cyano Androstanes" *USP 4831113 (*1989).

Verlan H. Van Rheenen, "Steroids Having an Enamide, or Cyano and Their Use" *CA 105:60816 (US-576590).*

Joel E. Huber ,Verlan H. Van Rheenen, "16α-Methylated-Δ17(20)-Corticoids as Intermediates" *USP 4704455 (1987)*

Verlan H. Van Rheenen "Ethynylation Of 16-Methylene-17-Keto Steroids" *USP 4614621* (1986).

Verlan H. Van Rheenen, "Cyanohydrin Process--Intermediates for Corticoids" *USP 4585590* (1986).

Verlan H. Van Rheenen, " 16-Methylene-17α-Hydroxy-Progesterones" *USP 4567001* (1986).

Verlan H. Van Rheenen, "Cyanohydrin Process" *USP 4548748* (1985).

Verlan H. Van Rheenen, Dae Y Cha, "Process to Prepare Stabilized Monolithiun Acetylide" *USP 4526720 (1985)/*

Verlan H. Van Rheenen "Spironolactone Process" *USP 4501695* (1985).

Verlan H. Van Rheenen, "Cyanohydrin Process Intermediates" *USP 4500461* (1985).

Verlan H. Van Rheenen, Joseph M. Timko, "16β-Methyl Steroid Process" *USP 4451404* (1984).

Verlan H. Van Rheenen , "Isomerization--Acylation Process" *USP 4443377* (1984).

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Edward J Hessler, Verlan H. Van Rheenen, "Synthesis of 16-Unsaturated Pregnanes from 17-Keto Steroids", *USP 4216159,* (1980).

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James B. Heather, Verlan H. Van Rheenen, "Phosphate-Catalyzed Acylation of Steroidal Tertiary Alcohols" *USP 4154748* (1979).

Verlan H. Van Rheenen, "Process for Preparing a 2(R) or 2(S) Tricyclic Lactone Glycol--Prostaglandins" *USP 4061657* (1977).

Keneth Paul Shephard, Verlan H. Van Rheenen, "Process for the Preparation of 17α-Hydroxy Progesterones and Corticoids from Androstenes" *USP 4041055* (1977).

Verlan H. Van Rheenen "Lactone Intermediates for Prostaglandins" *USP 3965118* (1976).

Verlan H. Van Rheenen "Tricyclic Lactone Glycol Sulfonates--Prostaglandins" *USP 3953473* (1976).

Verlan H. Van Rheenen "Bicyclic Lactones--Prostaglandins" *USP 3880887* (1975).

V. Van Rheenen, "Process for Preparing Lactone Intermediates" *USP 3823138* (1974).

Verlan H. Van Rheenen, "Conversion of 3-Enol Ethers of 3-Keto Steroids to the Corresponding 3-Keto-Δ4, 6β-(N,N-disubstituted)-Amino Methyl Compounds" *USP 3702848* (1972).

John M. Beaton, Jekishan R. Parikh, Verlan H. Van Rheenen, "Process for the Selective Reduction of 6-Methylene-3-Keto-Δ4-Steroids" *USP 3679715* (1972).

Verlan H. Van Rheenen, "Novel Chemical Process --Copper Catalyzed Oxygenation of Enamines" *USP 3661942* (1972).

Verlan H. Van Rheenen, "Process for the Conversion of 3-Enol Ether Steroids to the Corresponding 3-Keto-Δ4-6-Methylene Compounds" *USP 3642840* (1972).

Verlan H. Van Rheenen, "Steroidal 3-Keto-Δ1,4- Enamines" *USP 3629298* (1971).

Verlan H. Van Rheenen, "Process for the Preparation of Enol Ethers of 6-(N,N-Dimethyl Amino)-Methyl Steroids", *USP 3580935* (1971).

Verlan H. Van Rheenen, "Oxidation of Aldehydes to Ketones Employing Copper ions as Catalysts" *USP 3496197 (1970).*

Education

Ph.D., Organic Chemistry , University of Wisconsin, Madison, 1966.
B.A., Chemistry, Central College, Pella, Iowa, 1961.

Related Proceedings Appendix (37 CFR §41.37(c))

There are no related appeals or interferences pending during this appeal.